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Statement of the AGO Kommission Ovar, AGO Study Group, NOGGO, AGO Austria and AGO Switzerland Regarding the Use of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer

Harter, P ; du Bois, A ; Mahner, S ; Pfisterer, J ; Ortmann, O ; Marth, C ; Fink, D ; Hilpert, F ;
Wagner, U ; Sehouli, J

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DOI: <https://doi.org/10.1055/s-0035-1568169>

Other titles: Statement der AGO Kommission Ovar, AGO Studiengruppe, NOGGO, AGO Österreich und AGO Schweiz zum Einsatz der hyperthermen intraperitonealen Chemotherapie (HIPEC) bei Ovarialkarzinom

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-135368>

Journal Article

Published Version

Originally published at:

Harter, P; du Bois, A; Mahner, S; Pfisterer, J; Ortmann, O; Marth, C; Fink, D; Hilpert, F; Wagner, U; Sehouli, J (2016). Statement of the AGO Kommission Ovar, AGO Study Group, NOGGO, AGO Austria and AGO Switzerland Regarding the Use of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer. *Geburtshilfe und Frauenheilkunde*, 76(2):147-149.

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Key words

- ovarian cancer
- HIPEC
- statement

Schlüsselwörter

- Ovarialkarzinom
- HIPEC
- Empfehlung



Deutsche Version unter:
[www.thieme-connect.de/
ejournals/gebfra](http://www.thieme-connect.de/ejournals/gebfra)

Abstract

The AGO Kommission Ovar already published a statement in 2013, warning about the uncritical use of hyperthermic intraperitoneal chemotherapy (HIPEC) outside controlled studies. This statement has now been updated after the most recent literature was reviewed by AGO Kommission Ovar, the AGO Study Group, NOGGO, AGO Austria and AGO Switzerland. The authors conclude that HIPEC remains experimental. Its use is not recommended and should be rejected outside of prospective controlled trials.

Zusammenfassung

Bereits in 2013 wurde eine Stellungnahme der AGO Kommission Ovar, die vor dem unkritischen Einsatz der HIPEC außerhalb von kontrollierten Studien gewarnt hat, publiziert. Unter Würdigung der seither erschienenen Literatur wurde diese Stellungnahme nun gemeinsam von der Kommission Ovar, der AGO Studiengruppe, NOGGO, AGO Österreich und AGO Schweiz aktualisiert. Zusammenfassend kommen die Autoren zu dem Ergebnis, dass die HIPEC auch weiterhin als experimentell zu bewerten ist und ein Einsatz außerhalb von prospektiven, kontrollierten Studien nicht zu empfehlen und abzulehnen ist.

Because of the persistent uncritical use of hyperthermic intraperitoneal chemotherapy (HIPEC) to treat ovarian cancer in daily clinical practice, updating the statement issued by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) in March 2013 was a prime concern for our working group. It should also be mentioned in this context that, in cooperation with physicians from all medical specialties involved in the care of patients with ovarian cancer, we have developed an S3-guideline [1], in which the HIPEC method was rated by general consensus as an experimental concept, just as it was in our previous, more detailed statement [2].

When introducing new treatment methods into daily clinical practice there is a guiding rule (which applies to the introduction of both new drugs and new surgical strategies), whereby the assessment of such objective criteria as 'safety', 'feasibility', 'efficacy' and 'superiority compared to current standards' must be done gradually, consecutively, and in accordance with the criteria for evidence-based medicine before a new method can be implemented in daily clinical practice. In oncology the essential objective criteria are

'side effects', 'certain aspects of quality of life', 'progression-free survival' and 'overall survival'. It is extremely unusual to advocate introducing a new method "just like that" without any certainty of a proven advantage (or at least proven equivalence) as demonstrated in a comparative study. The justifications advanced for this are that those groups who use the new method are unable to carry out suitable comparative studies and that well known study groups are not doing trials. It should be noted that there are currently 8 registered international randomized trials investigating the use of HIPEC to treat women with ovarian cancer (NCT 01539785, 02124421, 01628380, 02328716, 00426257, 01539785, 01767675 und 01376752). This means that every group or hospital in Germany is free to participate in these trials in accordance with the rules of good clinical practice. The necessary funding to participate must be solicited either through the offices of the respective organizers of the trial or from other funding sources. The principle behind the allocation of public funds is that the concept must be persuasive and the expected outcome will be highly relevant – every trial must compete on this playing

received 1. 10. 2015
revised 1. 10. 2015
accepted 5. 10. 2015

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DOI [http://dx.doi.org/
10.1055/s-0035-1568169](http://dx.doi.org/10.1055/s-0035-1568169)
Geburtsh Frauenheilk 2016; 76:
147–149 © Georg Thieme
Verlag KG Stuttgart · New York ·
ISSN 0016-5751

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field. The experiences with the last two prospective randomized comparative studies into surgical issues in gynecologic oncology – the LION protocol on the benefits of lymphadenectomy in ovarian cancer and the DESKTOP trial on the value of surgery for recurrence – have shown that such projects are doable. The same yardstick must therefore be applied to the HIPEC method to treat ovarian cancer as is applied to every other new therapeutic strategy; the subjective convictions or interests of individual persons cannot be considered sufficient reasons to abandon standard therapies and introduce experimental therapies without further assessment.

A number of different studies have been cited as providing the theoretical basis for the intraperitoneal application of cisplatin in HIPEC; these studies are not directly comparable and are fundamentally different to chemotherapy administered intraoperatively on a one-off basis for a few hours. In classic intraperitoneal studies, various cytostatic drug regimens, dosages and usually therapies are administered whereby intraperitoneal application is combined with intravenous administration; application/administration is usually done over several cycles (usually over a period of 18 weeks). The advantage of HIPEC is supposed to be the “high” intraperitoneal dose administered intraoperatively. But it is important to note here that no benefits with regard to either progression-free survival or overall survival have been reported after a short-term dose increase, even in the context of high-dose therapy [3]; the same applies to a number of other studies which have evaluated dose-dense or/and dose-intensified regimens. The higher local bioavailability of chemotherapy can therefore not be cited as an argument for its presumed higher efficacy.

Unfortunately, while several publications are available on the use of HIPEC to treat ovarian cancer, only very few of them are prospective controlled studies. Most of these studies are single-center studies carried out in very heterogeneous patient populations (primary, recurrence); in a number of studies it is not possible to adequately characterize the study population because a detailed description of the population is lacking. One of the few studies which at least complies with the criteria defining prospective studies was published recently [4]. A total of 12 patients were included in the study which was carried out in Germany. With a median progression-free interval (PFI) to first recurrence of 16.7 months and a rate of complete resection of 58% achieved in surgery for recurrence, the initial prognosis for the selected patient population described in this study was very favorable. The median PFS of 13.6 months reported in this study is relatively low, given these prognostically favorable initial conditions; the median overall survival was not reported. Grade 3 impaired wound healing was noted in 25% of cases, and other higher-level complications were recorded in a further 25%. The reasonable conclusion drawn by the authors of this above-cited publication on HIPEC is that “this should not inspire an increase in the use of cytoreductive surgery [CRS] and HIPEC outside of clinical trials. Simple extrapolation of HIPEC from other solid tumors to EOC is inappropriate given the significant differences in tumor biology, prognosis, and available treatment options for patients with EOC. Further randomized trials can determine the efficacy of HIPEC before considering this approach a complementary element of treatment in patients.”

If these data are then compared with the recent literature on other controlled studies, the following facts must be stated: in the last published studies on systemic therapies, the median PFS was 11.3 months for patients treated with carboplatin/pegylated

liposomal doxorubicin (AGO-OVAR 2.9/CALYPSO trial [5]) or 12.4 months for patients treated with carboplatin/gemcitabine/bevacizumab (OCEANS trial [6]). Both of these studies were carried out in a patient population with far less favorable initial conditions; moreover, patients had either not undergone previous surgery (OCEANS) or to a far lesser extent (CALYPSO). In the last-mentioned study, 187 of 976 patients (15%) with recurrent platinum-sensitive ovarian cancer included in the study underwent surgery. Although this subgroup had a slightly less favorable prognosis as it also included cases with secondary recurrence, this subgroup most closely resembled the cohort of 12 patients described by Zivanovic et al. However, in the CALYPSO trial which used conventional chemotherapy without HIPEC the median PFS for all operated patients, irrespective of the success of the operation, was 18.2 months; in patients without radiologically measurable tumors median PFS was even slightly higher [7]. The complication rates also appear to be lower according to the data published for larger series who did not have HIPEC. In a recently published series of 217 patients who underwent surgery for recurrence without HIPEC, the median PFS was 20 months irrespective of the extent of residual tumor [8], and the reported rate of complications (grade 3+ in the Clavien-Dindo classification) was 11.6%. Even though such a comparison between different studies does permit any definitive statements and only allows hypotheses, it strongly underscores the fact that further prospective controlled studies, particularly larger and multi-center studies, are necessary and that such currently ongoing studies must be concluded **before** HIPEC therapy can be used as a valid therapy option in daily clinical practice.

Another publication from Germany with 90 patients has also reported data on the use of HIPEC to treat ovarian cancer recurrence [9]. The study reported a median survival of 35 months for patients in whom complete resection was achieved and who had HIPEC followed by systemic therapy. Here again the OCEANS trial (not a single patient had successful complete resection) can serve as comparison; in the OCEANS trial survival in both therapy arms was also 33–35 months, even though the median age in the published study on HIPEC was around 54 years and therefore considerably lower than in the studies without HIPEC used for comparison – and it is well known that age is an important prognostic factor in ovarian cancer. Despite the limitations attendant on such comparisons between studies, it should not be ignored that the overall survival rates after complete resection reported in other surgical series without HIPEC were significantly higher, ranging from 45 to 63 months [7, 10–14].

Our assessment of the currently available data on HIPEC therapy is supported by a systematic review published in the international literature. After a careful and detailed analysis of the currently available data, the authors in Spain came to the following conclusions: “The recently published retrospective data regarding the use of HIPEC for primary advanced and for recurrent ovarian cancer do not indicate any apparent advantage of this treatment in terms of the survival outcomes in these patients”; moreover, “based on the available information, neither gynecologic oncologists nor oncologic surgeons should offer this therapeutic approach to patients except in the context of a clinical trial as an experimental alternative” [15].

The Austrian Ministry of Health recently commissioned an assessment to investigate whether the use of HIPEC to treat colorectal, gastric or ovarian cancer should be included in the list of benefits covered by health insurance [16]. After an extensive analysis the authors arrived at the following recommendation

for all three tumor entities: “The inclusion of CRS + HIPEC in the list of benefits is currently not recommended. A repeat assessment is proposed for 2016 when it is anticipated that the results of currently registered phase III trials will be available.”

As indicated above, there are, at present, 8 registered randomized studies around the world. Such sufficiently large, prospective comparative studies are very much to be welcomed. Regrettably, as far as the authors of this statement know, only one hospital in all of Germany is participating in one of the aforementioned studies. The results of these studies should help us to understand the role of HIPEC better and to either include it in the armamentarium of ovarian cancer therapies or shelve it again. After careful analysis of the most recent literature the authors conclude that HIPEC remains experimental. Its use is not recommended and should be rejected outside prospective controlled trials.

Conflict of Interest



None.

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